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In the Specification

Please amend the paragraph beginning at page 32, line 19 as follows:

Cell Lines and Tissues. The breast cancer cell lines MDAMB435, MCF7, T47D, SKBR3, ZR75.1, MDAMB468, HS578T, MDAMB231 and the immortal human mammary epithelial cell lines (HMEC) MCF10A and HBL100 were obtained and maintained in culture according to instructions (ATCC, Rockville, MD). The two matched tumor cell lines, 21PT, derived from a primary tumor and 21MT, from the metastasis of the same patient, were propagated as described elsewhere. The breast cancer cell line, MW, was obtained from Dr. Renato Dulbecco. HMEC-H16N (immortalized with HPV) was kindly provided by Dr. Vimla Band. Cultured finite life span human breast epithelial cell strains 04372, 219-6, and 166372 were obtained from Clonetics (Walkersville, MD), and HMEC strains 1-26 and 3-14 were kindly provided by Dr. Steve Ethier. Finite life span HMEC 184, the immortalized HMECs 184A1 (passage 15 and 99) and 184B5 were kindly provided by Dr. Martha Stampfer, and grown as described ~~(http://www.lbl.gov/LBL-Programs/mrgs/review.html)~~ on the world-wide web at address lbl.gov/LBL-Programs/mrgs/review. Cell extracts from finite lifespan HMECs 70N and 81N were kindly provided by Dr. Khandan Keyomarsi. Mammary organoids were prepared from reduction mammoplasty specimens of women with benign or no abnormalities in the breast following collagenase digestion as described in Bergstraessar LM, (1993). Human mammary luminal and myoepithelial cells were prepared by progressive collagenase digestion of breast tissue, sedimentated to obtain organoids (ductal and lobulo-alveolar fragments), cultured short term, and finally highly enriched by using an immunomagnetic separation technique (Niranjan B, 1995).

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In the claims

Please cancel claims 2-6, 8, 15-17, 19, 26-29, and 33-37 without prejudice.

Please amend claims 1, 7, 9-12, 14, 18, 21, 22, 25, and 30-32 as follows:

1.   (Currently Amended) A method of diagnosing a cellular proliferative disorder of breast tissue breast cancer or ductal carcinomas *in situ* (DCIS) in a subject comprising determining the state of methylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids isolated from a sample comprising blood, plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes, bone marrow, or a combination thereof of the subject, wherein [[the]] a state of hypermethylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids as compared with the state of methylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids in comparable samples obtained from a subject not having the cellular proliferative disorder of breast tissue normal subjects is indicative of a cellular proliferative disorder of breast tissue breast cancer breast cancer or DCIS in the subject.

Claims 2-6.   (Cancelled)

7.   (Currently Amended) The method of claim [[6]] 1, wherein the duct cells are obtained by a procedure selected from ductal lavage, sentinel node biopsy, fine needle aspirate, routine operative breast endoscopy, nipple aspiration and core biopsy.

Claim 8.   (Cancelled)

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9.   (Currently Amended) The method of claim [[2]] 1, wherein determining the state of
      methylation comprises amplifying the nucleic acid by means of at least one sense primer
      and at least one antisense primer that distinguishes between methylated and unmethylated
      nucleic acids.

10.   (Currently Amended) The method of claim 9, wherein the primers hybridize with target
      polynucleotide sequences selected from SEQ ID NO:1-4, 15-18, 25-36, 41-48, 65-66, 73-
      76, 81-82 and combinations thereof.

11.   (Currently Amended) The method of claim 9, wherein the primers are selected from
      SEQ ID NO:7-14, 21-24, 37-40, 49-64, 69-72, 77-80, 85-90 and combinations thereof.

12.   (Currently Amended) The method of claim [[2]] 1, further comprising contacting the
      nucleic acid with a methylation-sensitive restriction endonuclease.

13.   (Original) The method of claim 12, wherein the methylation-sensitive restriction
      endonuclease is selected from the group consisting of MspI, HpaII, BssHII, BstUI and
      NotI.

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14.   (Currently Amended) A method of determining a predisposition to ~~a cellular proliferative disorder of breast tissue~~ breast cancer or DCIS in a subject comprising determining the state of methylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids isolated from a sample comprising blood, plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes, bone marrow, or a combination thereof of the subject,

    ~~wherein the nucleic acid is selected from the group consisting of Twist, cyclin D2, RARβ2, HOXA5, WT1, 14.3.3 sigma, estrogen receptor, NES-1 and combinations thereof;~~ and

    wherein [[the]] a state of hypermethylation of the nucleic acid(s) as compared with the state of methylation of CpG islands in the promoter of cyclin D2 nucleic acids in comparable samples obtained from ~~a subject not having the cellular proliferative disorder of breast tissue~~ normal subjects is indicative of a ~~cellular proliferative disorder of breast tissue~~ breast cancer or DCIS in the subject.

15-17. Cancelled

18.   (Currently Amended) The method of claim [[17]] 14, wherein the duct cells are obtained by a procedure selected from the group consisting of ductal lavage, sentinel node biopsy, fine needle aspirate, routine operative breast endoscopy, nipple aspiration and core biopsy.

19.   (Cancelled)

20.   (Original) The method of claim 14, wherein determining the state of methylation comprises amplifying the nucleic acid(s) by means of at least one sense primer and at least one antisense primer that distinguishes between methylated and unmethylated nucleic acid.

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21.   (Currently Amended) The method of claim 20, wherein the primers hybridizes with
       target polynucleotide sequences selected from SEQ ID NO:~~1-4,~~ 15-18, ~~25-36, 41-48, 65-
       66, 73-76, 81-82,~~ and combinations thereof.

22.   (Currently Amended) The method of claim 20, wherein the primers are selected from
       SEQ ID NO:~~7-14,~~ 21-24, ~~37-40, 49-64, 69-72, 77-80, 85-90~~ and combinations thereof.

23.   (Original) The method of claim 14, further comprising contacting the nucleic acid with a
       methylation-sensitive restriction endonuclease.

24.   (Original) The method of claim 23, wherein the methylation-sensitive restriction
       endonuclease is selected from the group consisting of MspI, HpaII, BssHII, BstUI and
       NotI.

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25.   (Currently Amended) A method for diagnosing a cellular proliferative disorder of breast

        tissue in a subject comprising:

        (a)   contacting a nucleic acid-containing specimen <u>comprising blood, plasma, lymph,</u>

                <u>duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes,</u>

                <u>bone marrow, or a combination thereof,</u> from the subject with an agent that

                provides a determination of the methylation state of <u>CpG islands in the promoter</u>

                <u>of cyclin D2</u> nucleic acids in the specimen, and

        (b)   identifying the methylation state of at least one ~~region of least one~~ <u>CpG island in</u>

                <u>the promoter of cyclin D2</u> nucleic acid, wherein [[the]] <u>hyper</u>methylation ~~state~~ of

                the at least one ~~region of at least one~~ <u>CpG island in the promoter of cyclin D2</u>

                nucleic acid ~~different from~~ <u>compared with</u> the methylation state of ~~the same~~

                ~~region~~ CpG islands in the promoter of cyclin D2 nucleic acids in <u>comparable</u>

                <u>samples obtained from</u> ~~a subject not having the cellular proliferative disorder of~~

                ~~breast tissue~~ <u>normal subjects</u> is indicative of ~~a cellular proliferative disorder of~~

                ~~breast tissue~~ <u>breast cancer or DCIS</u> in the subject.

Claims 26-29 (Cancelled)

30.   (Currently Amended) The method of claim [[27]] <u>25</u>, wherein the agent is at least one

        sense primer and at least one ~~antisene~~ <u>antisense</u> primer that hybridize<u>s</u> with a target

        sequence in the nucleic acid.

31.   (Currently Amended) The method of claim 30, wherein the target nucleic acid sequence

        is selected from SEQ ID NO:~~1-4,~~ 15-18, ~~25-36, 41-48, 65-66, 73-76, 81-82,~~ and

        combinations thereof.

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32.   (Currently Amended) The method of claim 30, wherein the primers are selected from the group consisting of SEQ ID NO:~~7-14,~~ 21-24,~~37-40, 49-64, 69-72, 77-80, 85-90~~ and combinations thereof.

Claims 33-34 (Cancelled)

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REMARKS

Claims 1-37 were pending prior to this Response, with claims 35-37 being withdrawn as subject to a restriction requirement. By the present communication, the paragraph beginning at page 32, line 19 has been amended to delete an active hyperlink. In the claims, no claims have been added, claims 2-6. 9. 25-27, 29, 26-29 and 33-37 have been cancelled without prejudice, and claims 1, 7, 9-12, 14, 18, 21, 22, 25, and 30-32 have been amended to define Applicants' invention with greater particularity. The amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1, 7, 9-14, 18, 20-25 and 30-32 are currently pending in this application.

The Objection to the Specification

The Office Action contains an objection to the Specification for containing an embedded hyperlink and/or other form of browser-executable code. To overcome the objection, by the present communication Applicants have amended the paragraph beginning at line 19 of page 32 to remove the active hyperlink.

In addition, the Examiner has requested that either the drawings of the description of the drawings be amended to set forth the proper sequence identifiers for each sequence. In response to this objection to the Specification, Applicants submit herewith copies of Figures 1-8 with mark-ups showing proposed amendments to Figures to recite the sequence identifiers for the sequences shown in the Figures. Applicant will provide formal drawings that include corresponding amendments to Figures 1-8 upon allowance of claims in this application.

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In view of the amendment and the marked-up copies of Figures 1-8 showing proposed amendments to add proper sequence identifiers, Applicants respectfully request reconsideration and withdrawal of the objection to the Specification.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 1-34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants disagree with the Examiner's assertion that the Specification fails to provide sufficient description to enable those of skill in the art to make or use the invention commensurate in scope with the previously presented claims. By the present communication, previously presented claims 2-6, 8, 15-17, 19, 26-29 and 33-34 have been cancelled without prejudice, rendering the rejection moot as to the subject matter of these claims. The rejection will now be discussed with regard to pending claims 1, 7, 9-14, 18, 20—25 and 30-32.

The Examiner asserts that the claims do not set forth the relationship between the nucleic acids of a subject and "the same" nucleic acids of a control that is not a comparison of nucleic acids between two individuals. To address the Examiner's concern, Applicants have amended claims 1, 16 and 28 to require detection of a state of hypermethylation in the patient's nucleic acid as compared with "the state of methylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids in comparable samples obtained from normal subjects." Thus, the "control" is not limited to breast tissue of a single normal individual, but is required to be representative of nucleic acids obtained from a plurality of normal, i.e., the absence of hypermethylation in CpG islands in the promoter of cyclin D2 nucleic acids in a broad population of normal subjects.

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Further, the Examiner asserts that there is no teaching or guidance in the specification that hypermethylation in an intron or exon of cyclin D2 would lead to decreased expression of cyclin D2 or be associated with breast cancer or any cellular proliferative disorder of the breast, thus causing those of skill in the art to allegedly engage in undue experimentation to practice the invention. However, the invention methods for detecting breast cancer or DCIS, as recited amended claims 1, 14 and 25, require detection of a state of hypermethylation of one or more CpG islands in the promoter of cyclin D2 nucleic acids in the subject's sample as an indication that the subject has primary breast cancer. Thus, hypermethylation in an intron or exon of cyclin D2 is excluded by the claim amendments.

The Examiner acknowledges that the Specification is enabling for an embodiment of the invention described as follows: "a method of detecting breast cancer of DCIS in a subject comprising obtaining nucleic acid from a blood, plasma, lymph, duct cells ductal lavage fluid, nipple aspiration fluid, breast tissue lymph notes or bone marrow specimen of a subject and determining the state of methylation of CpG islands of the promoter of cyclin D2 nucleic acids, wherein hypermethylation of CpG islands in the promoter of cyclin D2 is indicative of breast cancer in the subject" (Office Action, page 3). To reduce the issues and expedite prosecution, Applicants have amended independent claims 1, 14 and 25 to focus the invention on the subject matter that the Examiner has indicated is allowable. However, Applicants specifically reserve the right to pursue other embodiments of the invention in a subsequently filed application.

In view of the amendments and for the reasons discussed above, Applicants submit that the Examiner's concern that those of skill in the art would have to engage in undue experimentation in order to practice the claimed invention has been overcome Accordingly, reconsideration and withdrawal of the rejection of claims under 35 U.S.C. § 112, first paragraph, are respectfully requested.

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The Rejection under 35 U.S.C. § 102(a)

A.   Applicants respectfully traverse the rejection of claims 1, 25-27, 30, 33 and 34 under 35 U.S.C. § 102(a) as allegedly being anticipated by Ferguson et al. (*PNAS* 97:6049-6054, 2000; hereinafter "Ferguson"). By the present communication, previously presented claims 27, 33 and 34 have been cancelled without prejudice, rendering the rejection moot as to the subject matter of these claims. The rejection will now be discussed with regard to pending claims 1, 25, 26 and 30.

Applicants submit that the invention methods for detecting primary breast cancer in a subject, as defined by amended claims 1, 25, distinguish over the disclosure of Ferguson by requiring:

>determining the state of methylation of one or more CpG islands in the promoter
>of cyclin D2 nucleic acids isolated from a sample or specimen comprising blood,
>plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast
>tissue, lymph nodes, bone marrow, or a combination thereof of the subject,
>wherein a state of hypermethylation of one or more CpG islands in the promoter
>of cyclin D2 nucleic acids as compared with the state of methylation of one or
>more CpG islands in the promoter of cyclin D2 nucleic acids in comparable
>samples obtained from normal subjects is indicative of breast cancer or DCIS in
>the subject.

By contrast, Ferguson is absolutely silent regarding all elements of the invention methods for detecting breast cancer or DCIS as defined by amended claim 1 and 25. The Examiner asserts that Ferguson discloses that hypermethylation of the sigma promoter, for example, a CpG rich region of the 14.3.3 sigma gene promoter, is largely responsible for silencing of the sigma gene and occurs in a majority breast cancers. However, Applicants respectfully submit that Ferguson

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fails to disclose that hypermethylation of CpG islands in the promoter of the cyclin D2 nucleic acids, as compared with the methylation of comparable nucleic acids in normal samples, is indicative of primary breast cancer.

As Ferguson fails to disclose each and every element of claims 1, 25, 26 and 30, as would be required to establish anticipation under 35 U.S.C. § 102(a), Applicants respectfully request reconsideration and withdrawal of the rejection over Ferguson.

B.   Applicants respectfully traverse the rejection of claims 1, 25-27, 30, 33 and 34 under 35 U.S.C. § 102(a) as allegedly being anticipated by Esteller et al. (*Cancer Research*, 58:4515-4518; hereinafter "Esteller"). By the present communication, previously presented claims 26-27, and 33-34 have been cancelled without prejudice, rendering the rejection moot as to the subject matter of these claims. The rejection will now be discussed with regard to pending claims 1, 25 and 30.

Applicants submit that the invention methods for detecting breast cancer or DCIS in a subject, as defined by amended claims 1, 25, distinguish over the disclosure of Esteller by requiring:

> determining the state of methylation of one or more CpG islands in the promoter
> of cyclin D2 nucleic acids isolated from a sample comprising blood, plasma,
> lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph
> nodes, bone marrow, or a combination thereof of the subject, wherein a state of
> hypermethylation of one or more CpG islands in the promoter of cyclin D2
> nucleic acids as compared with the state of methylation of one or more CpG
> islands in the promoter of cyclin D2 nucleic acids in comparable samples obtained
> from normal subjects is indicative of breast cancer or DCIS in the subject.

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By contrast, Esteller is absolutely silent regarding all elements of the invention methods for detecting primary breast cancer as defined by amended claims 1 and 28. The Examiner asserts that Esteller discloses a method for determining the methylation state of CpG rich region of the GSTP1 gene promoter using methylation specific PCR in samples of breast tumor from a subject and compared to the methylation status of the nucleic acids in normal breast tissue.

However, Applicants respectfully submit that Esteller fails to disclose a method for determining the presence of breast cancer or DCIS in a subject by determining the presence of hypermethylation of CpG islands in the promoter of the cyclin D2 nucleic acids, as compared with the methylation of comparable nucleic acids in normal samples, as is required in the invention methods.

Therefore, Esteller fails to disclose each and every element of claims 1, 25 and 30, as would be required to establish anticipation under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection over Esteller.

In view of the above amendments and remarks, Applicants submit that all rejections of the claims are overcome and Applicants request favorable action on all pending claims. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.
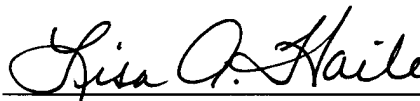
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The Commissioner is hereby authorized to charge any fees that may be associated with this Amendment, or credit any overpayment to Deposit Account No. 50-1355.

Respectfully submitted,

Date: October 3, 2003

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Enclosure: Marked up copies of Figures 1-8 (21 sheets)

(SEQ ID NO:105)

Cyclin D2 promoter, MSP primers
Accn. No. U47284   Promoter region analyzed: -1616 to -1394 bp

```
   1 gagctCGagc caCGccatgc cCGctgcaCG tgccagcttg CGcagcacat cagggCGctg
  61 gtctctcccc ttcctcctgg agtgaaatac accaaagggC GCGgtggggg tggggggtga
 121 CGggaggaag gaggtgaaga aaCGccacca gatCGtatct cctgtaaaga cagccttgac
 181 tcaaggatgC Gttagag            CGacCCtgct ggCGgacttc acCGcagtCG
 241 gctcccaggg agaaagcctg gcagagtgag gCGCGaaacC GgagggtCGg CGaggatgCG
 301 ggCGaaggac CGagCGtgga ggcctcatgc ctcCGgggaa aggaagggt ggtggtgttt
 361 gCGcagggggg agCGaggggg agcCGgacct aatccctcac tCGccccctc ccctccCGg
 421 gccatttcct agaaagctgc atCGtgtgg ccag                  tCGggCGgct
 481 tgtcagcaga tgcagggCG aggaagCGgg tttttcctgC GtggcCGctg ggCGggggaa
 541 cCGctgggag cctgccccC GgcctgCGgC GctgcacCGC GctgcacCGC GtCGccccac
 601 gggcccCGaa gagcccccag aaacaCGatg gtttctgctC Gaggatcaca ttctatccct
 661 ccagagagc acccccttc cttcctaata cccacctctc cctccctctt cttcctctgc
 721 acacactctg cagggggggg cagaaggaC Gttgttctgg tcctttaat CGggctttc
 781 gaaacagctt CGaagttatc aggaacacag acttcaggga catgacctta atctctggt
 841 atgCGgagtt gctattttct aaaatcaccc cctcccttat ttttcactta aggacctat
 901 ttctaaattg tctgaggtca cccatcttc agataatcta ccctacattc ctgatctta
 961 aatacaaggg caggaggatt aatgagtgaa attagagggc agaaatagga gtCGgtatt
1021 ttggCGtgct acacctacag aatgagtgaa attagagggc agaaatagga gtCGgtagtt
1081 tttgtgggt tgcctgtcCG ggccccctgg catgcaggct ggatggaggg agagggtgg
1141 gggtggCGg gggacCGCGt ttgaagttgg gtCGgggcag ctgctgttct ccttaataac
1201 gagaggggaa aaggaggag attgaaagga ggagCGGggg agaggggaga gagctaactg
1261 gaggaaaggg gaggaggaaac cagagCGggg aggCGgggga gagcaggga gagCGagacc
1321 cccagccagc ttgCGtcacC GcttcagagC Ggagtgag gcagcccCGa ggctctgctC Gcccaccacc
1381 agttttaagg ggaggacCGg tgCGagtgag gcagcccCGa ggctctgctC Gcccaccacc
1441 caatcctCGc ctcccttctg ctccaccttc tctctctgcc ccctccctc cccCGaaaac
1501 ccctatttta gccaaggaa ggagtcagg gaaCGctct ccctccccct tccaaaaaac
1561 aaaacagaa aaacccttt ccaggcCGgg gaaagcagga gggagagggg cCGcCGggct
1621 ggcc     gag
```

FIGURE 1A

MSP Unmethylated 223 BP

GT TATGTTATGT TTGTTGTATG

T AAAATCCACC AACACAATCA

Forward UM 22 BP MT 56 (SEQ ID NO: 21)

Reverse UM 21 BP MT 56 (SEQ ID NO: 22)

F M 19 BP MT 58 (SEQ ID NO: 23)

R M 20 BP MT 56 (SEQ ID NO: 24)

FIGURE 1B

Twist Promoter: Accn No. AC003986   *(SEQ ID NO: 106)*
Promoter Region analyzed: nts -51145 TO -51750

```
   1 cattgactg ggttcctc cacGaagag tgaacttctg cctctttCGa gcaccttcCG
  61 aggCGtagtc ctttgatgt tgggagCGt cagactgggt CGttgtagag gggaaggag
 121 ggcccagaag ggCGagagag caggcCGgga CGcaaatcct cagccccCGC GgCGCGccaC
 181 Gtcttcagaa aCGccaggac ctcCGggctg ggcCGcCGCG gtttggcctt tggaactcaa
 241 gggttCGtct acctgaccat tgggtggctc CGCGgttgac actttcttg gcatgccccc
 301 ccaccccCGCG ccacaccacc ccccagccc cagcaatcca aatCGgcccc aCGgacctag
 361 aggctcttg ggCGagatga gacatcaccc actgtgtaga agctgttgcc attgctgctg
 421 tcacagccaa tcCGgatggg gctgccaccCG tggccaggac agtctcctcC GacCGcttcc
 481 tgggctgCGc taggttCGg gggCGctgcc CGcaCGctcC GgCGgggaag gaaatCGccc
 541 CGCGccCGcC GgaggaaggC GaCGgaggag gaagggggag ggCGgctagg aggCGggtgg
 601 agggcCGgc CGcCGCGgggcc agg LCGtat t tgaatggttt gggaggaCGa attgttagac
 661 ccCGgaggaag ggaggtggga CGggggaggg ggactggaaa gCGgaaactt tcctataaaa
 721 cttCGaaaag tccctcctcc tcaCGtcagg cctccaagtc tgctgccccc aaactttcCG
 781 cctgcaCGga ggtataagag cctccaagtc tgcagctctC GcccaGtcc cagacacctc
 841 gCGggctctg cagcacCGgc acCGtttcca ggaggcctgg CGgggtgtgC GtccagcCGt
 901 tgggCGcttt cttttggga cctCGgggcc GcccttcccCG tcccctcccc ctccCGcctc
 961 cctccccCGcc tcccccCGCGC GccCGgccCG GcccCGGCG ccGgaggtccc tccCGtcCGt cctcctgctc
1021 tctcctcCGC GggcCGGcatC GccCGggcCG GccCGggcCG Ggggggaagc tggCGggctg
1081 aggCGccccCG ctcttctcct ctgcccCGgg ccCGGCGtCGc caCGCGtCGc CGctCGagag
1141 atgcagg aCGtgtccag ctCGccagtc tCGcCGgccCG aCGacagcct gagcaacagc
1201 gaggaagagc cagacCGgca gcagcCGCG agCGgcaagC GCGggggaCG caagCGgCGc
1261 aCGagcaggC GcaCGgCGgg gggccCGgCG gagCGgCGCG gggCGtCGga
1321 ggCGgCGaCG agcCGggcag ggcaagCGCG gcaagaagtc tgCGggctgt
1381 ggCGgCGCGg gCGgCGCGgg CGgCGgCGgC Ggcagcagca gCGgCGgCGg gagtcCGcag
1441 tcttaCGagg agctgcagaC GcagCGggtc atgccaaCG tgCGggagCG ccagCGcacc
1501 cagtCGctga aCGaggCGtt CGcCGCGCGg tccccaCGt gccctCGgac
```

FIGURE 2A

(SEQ ID NO: 106) (CONT'T)

```
1561  aagctgagca agattcagac cctcaagctg gCGgccaggt acatCGactt cctctaccag
1621  gtcctccaga gCGaCGgagct ggactccaag atggcaagct gcagctatgt ggctcaCGag
1681  CGgctcagct aCGccttctC Ggtctggagg atggaggggg cctggtccat gtcCGCGtcc
1741  cac▊▊cagg CGgagcccc caccccctca gcagggcCGg agacc▊▊gt aaggacCGCG
```

FIGURE 2B

Unmethylated 193 BP:

tt **TG**gatgggt tgttat**TGT**   FUM (3) 21 BP AT 58   (SEQ ID NO: 107)

c ctaaccC**A**aa **CA**ac**CA**acc   RUM (3) 20 BP AT 60   (SEQ ID NO: 108)

▊▊▊▊▊▊▊▊   FM (5) 20 BP AT 58   (SEQ ID NO: 109)

▊▊▊▊▊▊▊▊   RM (4) 19 BP AT 85   (SEQ ID NO: 110)

FIGURE 2C

RAR beta promoter, MSP primers   ACCN NO. AF157483 (SEQ ID NO: 2)

Promoter region analyzed: nt -196 to nt -357

```
   1 gtgacagaag tagtaggaag tgagctgttc agaggcagga gggtctattc tttgccaaag
  61 ggggaccag aattcccat gCGagctgtt tgaggactgg gatgcCGaga aCGCgatcGc
 121 tCGcatcagg gtttgtctgg gcacCGtCGg ggtaggatcC GgaaCGcatt CGgaaggctt
 181 tttgcaagca tttacttgga aggagaactt gggatctttc tgggaacccc cCGcccCGgc
 241 tggattggcC Gagcaagcct ggaaaatgca attgaaacac agagcaccag ctctgaggaa
 301 ctCGtcccaa gcccccatc tccacttcct ccccctCGag tgtacaaacc ctgcttCGtc
 361 tgccaggaca aatcatcagg gtaccactat gggtcagCG cctgtgaggg atgtaagggc
 421 tttttcCGca gaagtattca gaagaat     atttacactt gtcacCGaga taagaactgt
 481 gttattaata aagtcaccag gaatCGatgc caatactgtC Gactccagaa gtgctttgaa
 541 gtgggaatgt ccaaagaatc tgtcaggaat gacaggaaca agaaaaagaa ggagacttCG
 601 aagcaagaat gcacagagag ctatgaaatg acagctgagt tggaCGatct cacagagaag
 661 atcCGaaaag ctcaccagga aacttttccct tcactctgcc agctggtaa atacaccaCG
 721 aattccagtg ctgaccatCG agtcCGactg gacctgggcc tctgggacaa attcagtgaa
 781 ctggccacca agtgcattat taagatCGtg gagtttgcta aaCGtctgcc tggtttcact
 841 ggcttgacca tCGcagacca aattaccctg ctgaaggcCG cctgcctga catcctgatt
 901 cttagaattt gcaccaggta taccccagaa caagacacca tgactttctc agaCGgcctt
 961 accctaaatC Gaactcagat gcacaatgct ggattggtc ctctgactga cctgtgttc
1021 acctttgcca accagctcct gcctttggaa atggatgaca cagaaaacagg cctttctcagt
1081 gccatctgct taatctgtgg agacCGccag gaccttgagg aacCGacaaa agtagataag
1141 ctacaagaac cattgctgga agcactaaaa atttatatca gaaaaagaCG accaagcaag
1201 cctcacatgt ttccaaagat cttaatgaaa atcacagatc tcCGtagcat cagtgctaaa
1261 ggtgcagagC Gtgtaattac cttgaaaatg cttgaagtcctg gatcaatgcc acctctcatt
1321 caagaaatgc tggagaattc tgaaggacat gaaccccttga cccaagttc aagtgggaac
1381 acagcagagc acagtcctag catctcacc agctcagtgg aaaacagtgg ggtcagtcag
1441 tcaccactCG tgcaataaga ca
```
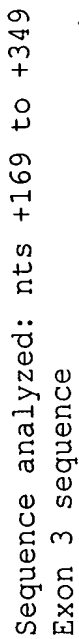
FIGURE 3A

ACCESSION

Homo sapiens serine protease-like protease (nes1) mRNA, complete cds

AF024605   (SEQ ID 4A)

```
   1 accagcggca gaccacaggc aggcagagg cacgtctggg tcccctccct ccttcctatc
  61 ggcgactccc agatcctggc catgagagct ccgcacctcc acctctccgc cgcctctggc
 121 gccgggctc tggcgaagct gctgccgctg ctgatggcgc aactctgggc cgcagaggcg
 181 gcgctgctcc cccaaaaacga cacgcgcttg gacccgaag cctatggcgc ccgtgcgcg
 241 cgcggctcgc agccctggca ggtctcgctc ttcaacggcc tctcgttcca ctgcgcgggt
 301 gtcctggtgg accagagttg ggtgctgacg gccgcgcact gcggaaacaa gccactgtgg
 361 gctcgagtag gggatgatca cctgctgctt cttcaggcg agcagctccg ccggacgact
 421 cgctctgttg tccatcccaa gtaccaccag ggctcaggcc ccatcctgcc aaggcgaacg
 481 gatgagcacg atctcatgtt gctaaagctg gccaggcccg tagtgccggg gccccgcgtc
 541 cgggccctgc agcttcccta ccgctgtgct cagcccggag accagtgcca ggttgctggc
 601 tggggcacca cggccgcccg gagagtgaag tacaacaagg gcctgacctg ctccagcatc
 661 actatcctga gccctaaaga gtgtgaggtc ttctaccctg gcgtggtcac caacaacatg
 721 atatgtgctg gactggaccg gggccaggac ccttgccaga gtgactctgg aggccccctg
 781 gtctgtgacg agaccctcca aggcatcctc tcgtggggtg tttaccccctg tggctctgcc
 841 cagcatccag ctgtctacac ccagatctgc aaatacatgt cctgatcaa taaagtcata
 901 cgctccaact gatccagatg ctacgctcca gctgatcccag atgttatgct cctgctgatc
 961 cagatgccca gaggctccat cgtccatcct cttcctcccc agtcggctga actctcccct
1021 tgtctgcact gttcaaacct ctgccgccct aaacatctcc cctctcacct
1081 cattccccca cctatcccca ttctctgcct gtactgaagc tgaaatgcag gaagtggtgg
1141 caaaggttta ttccagagaa gccaggaagc cggtcatcac ccagcctctg agagcagtta
1201 ctggggtcac ccaacctgac ttcctctgcc actccccgct gtgtgacttt gggcaagcca
1261 agtgccctct ctgaacctca gtttcctcat ctgcaaaatg ggaacaatga cgtgcctacc
1321 tcttagacat gttgtgagga gactatgata taacatgtgt atgtaaatct tcatgtgatt
1381 gtcatgtaag gcttaacaca gtgggtggtg agttctgact aaaggttacc tgttgtcgtg
1441 aaaaaaaaaa aaaa
```

FIGURE 4A

cCGcagaggC GgCGCtgctc cccaaaaCG acaCGCGctt ggac▓▓CGa▓▓ ▓▓▓▓▓▓▓ ▓GtgCGC
GCGCGgctCG cagccctggc agtctCGct cttcaaCGgc ctctCGttcc actgCGCGgg tgtcctggtg gaccagagtt
gggtgctgaC G▓▓▓▓▓▓ ▓▓ ▓▓▓▓▓▓▓

(SEQ ID NO: 95)

Sequence analyzed: nts +169 to +349
Exon 3 sequence

FIGURE 4B

Unmethylated 128 BP

tTGtagaggT GgTGttgttt   Nes1 FUM 20 BP AT 56   (SEQ ID NO: 77)

CACAcaat aaaaCAaaaa.acCA   Nes1 RUM 22 BP AT 56   (SEQ ID NO: 78)

▓▓▓▓▓▓▓▓ ▓▓▓ BP

▓▓▓▓▓▓▓▓▓▓▓   Nes 1 FM 20 BP AT 56   (SEQ ID NO: 79)

▓▓▓▓ ▓▓▓▓▓▓▓   Nes1 RM 20 BP AT 58   (SEQ ID NO: 80)

FIGURE 4C

HOX A5 Promoter 3' to 5'

AC004080 (SEQ ID NO: 96)

```
16321 accaagagag actgggagag aagagagggg ggacCGagag aagagagggg cCGCGtcccc
16381 gCGgtCGCGt ggatttagaa aaaggctggc cttatgtgca tttaccatga gcttgCGcat
16441 ccagggtag  atctggggtt gggCGggCGg CGcCGggctC GgctCGctct gCGcactCGC
16501 ctgctCGctg ctggcagggg CGtcctcctC GgctCGgaC  GcCGtgccaa cccctctct
16561 gctgctgatg tgggtgctgc CGgCGtCGgc CGaggCGCGc aCGGCGgagc ttagggagtt
16621 tttccCGcCG tggtggctgt CGctgcCGgg CGaggggggcc aCGGCGgagc agggcagCGg
16681 atCGggctga ggagagtgCG tggaCGtggc CGgctggct  tacctggct  CGgCGggCGc
16741 CGCGctggCG ctggcagCGt agctgCGggC GCGctctcCG tacctggct  ggcCGggagcc
16801 CGagCGgcCG aCGctgagat ccatgccatt gtagcCGtag cCGtacctgc CGgagtgcat
16861 gctCGcCGag tccctgaatt gctCGctcaC Ggaactatga tctccataat tatgcaactg
16921 gtagtcCGgg ccatttggat acaaaataag aaatgagttt acaaaataag ███ ttg
16981 tttttgata  tgtgtgcttg CGCGgtCGtt tgtgCGtcta tgtCGtcta  tagcaccctt
17041 gcacaattta tgatgaatta tgggacatgt acttggttcc             ctcctaCGta
17101 ggcaccaaa  tatgggtaC  caCGtgcttt tgttgtcttt tgttgtccag tCGtaaatcc
17161 tgcctgatga cctctagagg taaactCGtg cactaatagg ggagttgggt ggaggCGagg
17221 gggtggCGC  GCGGCgcccCG ggCGCGtgcc tgcCGgccagt tgcCGcCGtt cagcCGgact
17281 CGagCGccac cCGctggagg CGcCGccagt CGcccagctt cCGacCGggg gctgcaaggg
17341 cCGgggtCGa attgaggtta cagcccatta tggcaaaatt attgcatttc cctCGcagtt
17401 ccattaggat gtaccaattg ttagccCGtc agctgcCGat CGCGCGccCG gCGaggatgc
17461 agaggattgg
```

FIGURE 5A

Promoter region analyzed: nts -97 to nts -303

Complement- 5' to 3' (SEQ ID NO 97)

```
ccaatcctct gcatcctCGc CGggCGCGCG atCGgcagct gaCGgcctaa caattggtac atcctaatgg
aactgCGagg gaaatgcaat CGggCGg aatttttgca taattggctg taaa ctcaat tCGaccccCGg cccttgcagc
cccCGgtCGg aagctgggCG atgagccctg cctggcagCGt gtcgcgtcg agtcCGgctg aaCGgCGgca
actggCGgCG ggcaCGCGcc CGgggCGCGC GCGccaccc.cctCGcctcc accaactcc cctattagtg
caCGgagttta cctctagagg tcatcaggcaggattaCGa ctggacaaca aagcaCGtg attCGaagtC
Gtacccata tttgggtgccta CGtgtgcgag acaigtgcca gtcatttcca taattcatca
taaattgtgc aagggtgcta agct cttatttgt aaac ggg aaatgg ccCGgactac
tatcaaaaacaa agct cttatttgt aaac ggg aaatgg ccCGgactac
cagttgcata attatggaga tcatagttcC Gtgat CGagc aattcagga ctCGgCGagc atgcactcCG
gcaggtaCGg ctaCGCGg aatggcatgg atctcagCGt CGgcCGCGctCG ggctcCGgcc acttggtct
CGgagagCGC GcccGCGg CGccagCGCg CGccagcGCG gCGccCGcCG agcc
caCGtcca CGcactctcc tcagccCGat
```

FIGURE 5B

UnMethylated 213 BP

tTGgtTGg aagttgggTG FUM 18 BP AT 56 (SEQ ID NO: 71)

gtaTGtg attTGaagtT Gtatt (SEQ ID NO:98)

aataC AacttCAaat caCAtac RUM 22 BP AT 56 (SEQ ID NO:72)

FM 18 BP AT 58 (SEQ ID NO:69)

(SEQ ID NO:99)

taCGtg attCGaagtC Gtat RM 20 BP AT 56 (SEQ ID NO:70)

FIGURE 5C

should be corrected in the seq. listing

tHAgcgg[?]tggcg+tcg

Sequencing 307 BP

ggag ggaattaagt atatgtt

Hox A5 Seq. F 23 BP AT 56 (SEQ ID NO:73)

Hox A5 Seq. A (SEQ ID NO:108)

Hox A5 Seq.R 21 BP AT 56 (SEQ ID NO:74)

Hox Exp F 20 BP AT 60 (SEQ ID NO:75)

ccaggta cagccagccg gc (SEQ ID NO:107)

Hox Exp R 18 BP AT 62 (SEQ ID NO:76)

FIGURE 5D

Homo sapiens 14-3-3 sigma protein promoter and gene, complete cds.
ACCESSION No. AF029081 SEQ ID NO: 1021

```
   1  ggatcccagc  ctgcccctcc  acttctctcc  caagccagt   cccggcatgg  gtgggttatg
  61  ctcatgctgg  caatacttga  aacgggttta  ttaatgctgg  gtattttgca  caattttata
 121  gacctctttt  ctacatagtc  tttttaaat   ggaaggagaa  aatgtcagcc  acattactgt
 181  ctgtgtagtg  ccaggtgaag  ggttatcaga  aggctggttg  gttttaataa  gtttattcca
 241  agagaccttc  tggctgaat   gagtgagagt  gtgtgtgcat  gtgtgtgtgt  gttcatgtgt
 301  gccctgtatg  aatgttggctg gctcccagat  cccctgggct  gccccctgcc  ccatcccctt
 361  tgagtatcag  aagcactctg  agccaagggg  acaggggca   cgtgcactgg  tcacgagaaa
 421  accctgggct  cccactgggg  ctcagccag   cctcctatct  ttccttcttc  tatggacttc
 481  agacagccag  tgtctgggga  ctctgccact  ctaccccag   cctacccac   cagcccccag
 541  gtgaggcttc  cagctgggac  ctgcccagac  aggctgagcc  tgggcgtggt  gggtggggtg
 601  atggctctgg  ggagcggctg  ccatcctaca  agccacaccc  cctcctctga  gctctgaata
 661  tgggaccag   tgccaggagc  tggaagacaa  ggtgtttctg  ccaaacggga  cctccatcca
 721  gagaaaagga  agaaggtgca  gggtgggcca  agagcaggt   gaaggttggc  ctgagtctgg
 781  gccggaaact  cagaggatgt  ttctcctctg  ctgggagctg  tagtttctta  tcaaaataga
 841  tattgttcca  ccatccccct  cctggccct   tcaagtgggc  tgaagccttg  gaaagtgaca
 901  taggaagtcc  ccagatcttg  ccttctcac   tccagaggct  agtggtcaca  gacagctggg
 961  aatggcagcc  acagagggtc  cctctggaga  aacagcttca  cccagcctc   agggccctgg
1021  gcatcactgc  agtggccctg  ggaggtgagg  aagaagctgg  ctagaggag   gggctcccac
1081  ctacctttta  tttaagccag  tattctttgt  tcctgcttgt  aataaaactt  cagtttataa
1141  gagttgcttt  gctttggttt  ggttttttgtt tgctttttcct ttgctgaggc  cccaactggg
1201  agccctctgt  tctttcagac  aaatttggtt  cttttctggg  gagactgtga  gaaggcaggc
1261  agccagtga   tctggctaca  tttccctca   cctgcctgga  gctctgtccg  ctggaggaag
1321  agcagagagg  gctgcggctg  agccccatg   ggcacgtgaa  aagaggccat  cctgtcccct
1381  ctttgtcccc  tccaccttcc  cctgcctcag  gggcttggag  accccaaatt  cttcttccct
1441  actgcctttc  cactccgatc  cccaatgagt  gcccagctaa  gaaaatgttt  gagacagtag
1501  attccagttt  gagagccgga  gcttccctgg  ctaccacctc  caacctgggc  accaggccc
1561  agccagacaa  ctcataacac  tggcccacct  ctctggtatc  tccctcagga  ggacacctgt
```

FIGURE 6A

(SEQ ID NO: 102 (cont'd))

```
1621  caggattttg  ccatctcctg  cacagctga   gggagctaa   caggcctctt  tgcagagggt
1681  tagctggtaa  gaccgtttct  tccctgtcgg  ccagcactgc  ccgctcccct  ccacacacca
1741  tctcatcctc  atcgcatgcc  tcgccaaccc  catggagccc  gtccatctgt  ctggtgtgtg
1801  gtgcggtgtg  tgtgctggtg  gtggtaggt   ctccagggac  tccccgctaa  gcagaaggat
1861  cgggatatag  ggcaaggcta  aaagcccagc  cccattgtgg  actgaggaag  tacgttcgcg
1921  cagagcagct  ctccagctgg  aagagaggt   ggaggtgag   gctgggggga  ggatggcgaa
1981  cctgccctga  ggtgcttggg  tctgtgctgg  tggggtcctg  gtatgcaggg  gccaccggtc
2041  actaacactc  ttatgtcctg  gctttctgtc  ccgctgagc   tttctctcac  ccgcccgttt
2101  tctctcctgc  ttcattgcct  gctgcctaag  ccttggccct  tctctcgggc  agaggcaggt
2161  gctgtggcag  caactcctcc  caccacggg   ccctgcagg   ccgcctcct   cctcccaggc
2221  ctgctaaccc  tctctcttct  ccttcttgc   tgtcctgccg  gggatctcca  gtgtgtgcgg
2281  gggcttaagg  acctcctgag  gaccgctgct  ctctgcctct  ccaggaatgg  cctggggga
2341  gccaggcacc  cggcacctcc  acctgcctaa  cctgtggccc  atctgccacc  atctgtgcct
2401  acagggtctg  ccccccagcc  tgccggcct   gtgtgtctc   taggaccca   tagggggcag
2461  gggctggcct  ctttgcccca  ttcccgctcc  atgccggcca  gagtgtagaa  agccataacg
2521  cacgcagcca  tcagcacaat  aatgtgactc  tacgctgata  tgctccctct  ctcctccact
2581  gacttcccct  tcccggattt  gtgaggtgtc  aagactagga  atctgccctt  agagcctgcc
2641  cctccacccc  ctcagatcag  gcatagccat  agtcaagccc  agcaggtttc  ctcaggagct
2701  gtctgggtgt  ttgatgtgg   atgacgctgc  tgaacaagtt  tggtgactgt  tctaagcaca
2761  actggcttga  tactgttccc  acggcctgtc  cacctcccac  cccaaccct   ccaccagagt
2821  aggtaggatg  taggaggt    gcgtgccgcc  tttgctctag  gcactgaggg  accaagctag
2881  ccgtgcacag  cccatacac   ttcaggggcg  taaaggaaag  agctgagcca  aggaaaatca
2941  gctgagccca  ggctggggg   ctgcttgtct  gctatcctgt  accttttttt  tttttaacca
3001  aaataaagat  tcccctcttc  ttgccatacc  attggctgtc  tggtggcgcc  tttactttgg
3061  ggccaggga   tggacctgc   agtgggcgtg  tggaacatat  ggctccccct  cgctcccagc
3121  tttcttccag  ctggccagtg  ctgctctgga  gatttacaag  cacaacgaag  ccaggaggga
3181  cacaggaaaa  gtggctgaca  tcctttcac   tctgcccctc  cagaactctt  gtgtctcaatt
3241  ccagacacca  cccagcctta  gctgacctct  ggattctgat  aggtcccagt  gcaggctgag
3301  acagagggtt  taactccagt  ttgggactgc  cataccatg   aactgagccc  agcccaggt
3361  aacgatctca  tgaaacttc   tctctcccca  gttgctgcac  tacatcaaga  tacacacatg
3421  tgcatacact  gtactatggg  ctaaaaaat   acgtaccgct  accgttcagc  aaggggcttgc
```

FIGURE 6B

(SEQ ID NO:102(CONT))

```
3481  cgagtcccgg  gcccatttc  tcatcttaac  ctgtgaggag  gatgatgtca  gccttttac
3541  agatgaggga  actgagactc  aaggaagaaa  caggagctgc  ccaaggtcac  ccagctggca
3601  aagcagcaaa  tcccagatcg  gaacctgatc  tctgccccga  gctctgagcc  atctgcacta
3661  cccaaggaat  gaatacagcg  gtgggaggat  gagatcttgg  agaaaccta  aaattagaga
3721  atgtcatagc  cagtagaggg  cttagagttg  atctggccca  gcctccttgt  tttactgatg
3781  gagaaattga  agcccagagg  caggaaggga  cctgcccaag  gccttataac  agagctggga
3841  tgcagtccca  cactctgacc  tcattccatt  ctctctccat  aaattctgca  ctgtctctag
3901  actggactgg  tttagatgtg  ggatactcta  aacagcagtg  ccttcaagag  aaaaagaatc
3961  agaactacga  atcacttaaa  agtaatgtaa  gctactctgg  gcacactgcc  tatgggtcg
4021  ccctgctcca  caggagcca  caaaaataat  taaatataatt  taatatccct  tcccaaaggt
4081  aaccagtaaa  gtaagctctt  ggctaggtaa  ctgactctt  gttcacaact  agccagtggg
4141  aaaaggtgct  agagcttcct  ctggccacct  gtttaatttg  atcattccaa  gacagaaaca
4201  tttcttagga  agttctttct  agaatctacc  tggtgtccct  cccactgcta  tcagagccct
4261  gtcctctgtc  ctcagtggag  gtagagagca  aatggttgct  gctttcttca  tcacaaccct
4321  tcaaagccta  ttattaccag  ctaagaagga  ttggttgact  atgggccaga  gccccctgagc
4381  ctgctggtag  aatggatgct  gtacaggagg  gtggggaggt  agcaggcaga  atgaggaaag
4441  ccccttgag  ctgcaacccc  agctcctgtc  ctgctgactc  agacagctga  ctgtggagct
4501  ccatgccctg  ccaggggctg  ctgcctcctg  ccgtctgag  ctcctgaact  tgggaaatgg
4561  aggcccagag  gcaaagggag  gtacctgaga  caggaactga  gtcaggatca  acaggccaga
4621  gcggcagga  ggtatcaggc  agcctggctc  ccagatgcac  ccctgagctc  cagcaggga
4681  ggagtaggaa  tgaaggggct  tccttgccct  tgctcatggc  tatgcggagg  gcgtgaacca
4741  ccaccaggtc  ctctggctta  agtggcggga  agcaaatggt  ccctccctgg  actcaggctc
4801  caaagttcct  gggcctgcct  tccaggttcc  cagtgtcctg  ggatctccag  ctttccccag
4861  gacttgggga  agccccggct  ggatgactag  tacaaatgaa  ggcccctgag  gttccaggac
4921  ctgctgaggt  cacaggaata  tcctagatca  agcttgtcca  acccacggcc  cacaggctgc
4981  atgtggccca  gaatggcttt  gaatgcagcc  caacacaaat  tagtaaactt  tcttaaaaca
5041  ttatgagatt  tttttgcaaa  tttttttttt  ttttttagct  catcagttat  tggtagtgtt
5101  ggtatatttt  atgtgtggcc  caagacaatt  cttccaatgt  ggccagggga  agccaaaaga
5161  ttggacacgc  ctgtcctaga  tggagaggaa  ggaggcagtg  ctgacacat  ctggccattc
```

FIGURE 6C

SEQ ID NO:102 (CON'T)

```
5221  atccatctgg agagagaagg ctatggcaa  actgcttcct ctcccctgta gacaccagc
5281  tgggaaggtc tggcctttgg taagtcctgg cttgggtcc  ttcctcattt cacagaacct
5341  aactctatgt tagtgctttg tgagtatatg ttgatcataa taaagttgac gggatttttt
5401  cacatgataa taatagttgt catctggccg ggcatggtgg cttatgccta taatttcagc
5461  actttggaag gctgaggcag gtggatcact tgaggtcagc tgttcgagac cagcctggcc
5521  aacatggtga aaccacatct ctacttaaaa aaaaaaaaa  tacaaaaatt agctgggtgt
5581  ggtggtgcac ccttgtaatc ccagctactc gggaggctga ggcaggagaa tcacttgaac
5641  ccaggaggtg gaggttgcag tgagctgaga ttgtgccact acactccagc ctgggtgaca
5701  agagcgaaac tccgtctcaa aaaaaagaa  aataataata ataatagttg ccatccattc
5761  tactgtgctt tccattaact cgtgtaatcc tcacaagtcc catttatag  ttacaggaac
5821  tgaggctcac agagcttaaa tcacttggcc aaggccacaa acagctataa gaattacatt
5881  taggcagtct gattccaaag atactagtct attctgtatc tcatagacaa acaatacata
5941  ttcactttt  tgttgttgtt ttgttttgag acggagtctt gctctgtcac ccaggctgga
6001  gtgcagtggc gccatctcgg ctcactgcaa cgtccgcctc ccggttcaa  gcgattctcc
6061  tgcctcagcc tcccgagtag ctggactac  gggttttcct gggttagcca gatggtctc
6121  ttgtatttt  agtagagaca gggtttcct  gggttagcca gatggtctc  gatctcctga
6181  ccttgtgatc cacccacctc agcctcccaa agtgctgaga tgacaggcgt gagccaccgc
6241  gtccgaccta tattcactat ttataaattg gagagaataa gaaaatcaaa agggccaggt
6301  gtagtgactc acacctgtaa tcccagcact ttggaagcc  aaggcaggag gattgcttga
6361  accagaaagt tcgagaccag cctgggcaac atggtgagac cctgtctcta caaaaaatac
6421  aaaaaattagc tgggcgttgt ggtgagcacc ttattcttag gaagctgagg caggaggatc
6481  acctgaggcc aaggaggttg agactgcagt gagctgtgat cataccactg tacttcagcc
6541  tggacatcag agtaagaccc tatctctaaa aaggaaattg agaagaaaga aaatcaaagg
6601  gaagcaaaat cactcactct cactacctca agatacctc  tagaagttgg tattttagtg
6661  tggttcctat tgtttctgt  gtcagttctc tgatttgagc aaaatctttg ggagctcaaa
6721  cttaaaatcc ccttacttc  cttggaaacc ctgtagcatt agcccagaca tgtccctact
6781  cctccttgtg gcaaagagaa ggatctcgtc tttgtccc   agagttctgg cctaagcctc
6841  cctccaggag ggaagatgag tgttcagaca ctcagagtag ctgggggaga cacaggcctg
6901  tgaaattatc ctggctcaac tattagtcg  gcagaatccc agtgaaggga gccctacctc
6961  tgagcccat  ctaagctttg gctatgggtg gggcagataa gcaggaatcc atccctatag
```

FIGURE 6D

(SEQ ID NO: 102 (CON'T))

```
7021  gctcaatgcc  aacacccta  ggtgaaactc  ttgatgaaac  ttgaggccag  ggctccggca
7081  agcaggaaa   gaacgttggc  aacagaggtc  tccatctctg  aggactctgc  caggggtcag
7141  agatgggca   atggtcaaaa  ggaaggaaca  ggccaggcac  agtggctcat  gcccataatc
7201  ccagcactt   gggaggctga  ggcaggagga  tcgcttgagc  ccaggagttt  gagacctgcc
7261  tgggcaatgt  agtgagatct  gctctctatt  taaaaaaaaa  aaaaaggaaa  gaacaagtaa
7321  acttctgaga  aacaggctgg  gggaggcatc  acgtagctgg  aattgctgcc  ccataaaaca
7381  gaatggtatg  tgtcactgcc  acctccctt   ctcagtcctc  tctctcccca  ggttgctagc
7441  gtcccctgg   gggatcaaac  tggactgctt  cccagcctca  gacagagagc  agtctgagtc
7501  aggcaggaaa  gtgggacagc  cgggagctg   gaccccaccc  tctgtgagcc  ccgctggtac
7561  ctgatggcat  gtggcttgga  gagggcaggt  gacctggcgt  ggagggccag  agggtaaatc
7621  ctcaaacaag  tggcaacagg  ccaccaactt  gaaagggaaa  attgtgtagt  gatgggaaat
7681  gtgtccaaca  aacctactgg  gtgactaatt  acaaaggctg  ggctggagct  tcagaggctg
7741  cttgttaaac  acttcattaa  gcggcactct  gaaagctgcc  acctgcgcat  tctgggagct
7801  cagagggac   cctgaggggg  aatgaggcct  ggaggatgga  accatcttca  ggtagactga
7861  gaaggagcct  ggatctcact  tccaaacaca  gtctggagct  cataggtcag  aggcctcaat
7921  gggagaaaag  ctaaaggaag  agggtgcaga  aaggagtttc  agggaattgg  tggctatgtg
7981  actttgagca  aatctccaccc  ctctctgaga  cttagtgttc  ccatctctat  ggtcctgtgt
8041  gtgtcacaga  gacatggtgg  ggattaaatt  cgatcgtgat  atgaaagtgc  ttggaaact
8101  ccatgccct   acctaaacat  gagttatcct  cacctgaacc  aagggggaa   gttacctggc
8161  aggattagga  accccatcct  cctgaacctt  tatgggctct  gtcgaggctg  aagcagccag
8221  gggctaaagc  cagtccttag  cccctggaag  ggcactgtga  aagtggatct  gatttgagaa
8281  gccgtttcct  gatgtgggca  gccatgtgat  gccagccccg  aacaagaggg  ggcagcctgg
8341  agcctgaaa   ggtgccagtg  caggtgggc   ccacgcccag  atttctcctg  ctgactgttc
8401  tgatgattca  ccccacatc   ccagccttt   tacctttact  gcagagccgg  aaaggtgtg
8461  gggaagagag  gagagggagg  caggtcttgg  gccctgtcc   cgcccctgc   tcctccccac
8521  ccttctctgg  gcctggccac  ccagccaaaa  ggcaggccaa  gagcaggaga  gacacagagt
8581  ccggcattgg  tcccaggcag  cagttagccc  gccgcccgcc  tgtgtgtccc  cagagccatg
8641  gagagagcca  gtctgatcca  gaaggccaag  ctggcagagc  aggccgaacg  ctatgaggac
8701  atggcagcct  tcatgaaagg  cgccgtggag  aagggcgagg  agctctcctg  cgaaagagcga
```

FIGURE 6E

(SEQ ID NO: 102 (CONT))

```
8761   aacctgctct  cagtagccta  taagaacgtg  gtgggcggcc  agaggggctgc  ctggagggtg
8821   ctgtccagta  ttgagcagaa  aagcaacgag  gagggctcgg  aggagaaggg  gcccgaggtg
8881   cgtgagtacc  gggagaaggt  ggagactgag  ctccagggcg  tgtgcgacac  cgtgctggggc
8941   ctgctggaca  gccacctcat  caaggaggcc  ggggacgccg  agagccggt   cttctacctg
9001   aagatgaagg  gtgactacta  ccgctacctg  gccgagtgg   ccaccggtga  cgacaagaag
9061   cgcatcattg  actcagcccg  gtcagcctac  caggaggcca  tggacatcag  caagaaggag
9121   atgccgccca  ccaaccccat  ccgcctgggc  ctgccctga   acttttccgt  cttccactac
9181   gagatcgcca  acagccccga  ggaggccatc  tctctgccca  agaccacttt  cgacgaggcc
9241   atggctgatc  tgcacaccct  cagcgaggac  tcctacaaag  acagcaccct  catcatgcag
9301   ctgctgcgag  acaacctgac  actgtggacg  gccgacaacg  ccggggaaga  gggggcgag
9361   gctccccagg  agccccagag  ctgagtgttg  cccgccaccg  cccgccctg   tcccctaggc
9421   tcccccaccc  tgccgagagg  actagtatgg  ggtgggaggc  cccacccttc  tcccctaggc
9481   gctgttcttg  ctccaaaggg  ctccgtggag  agggactggc  agagctgagg  ccacctgggg
9541   ctgggatcc   cactcttctt  gcagctgttg  agcgcaccta  accactggtc  atgcccccac
9601   ccctgctctc  cgcacccgct  tcctcccgac  cccaggacca  ggctacttct  ccctcctct
9661   tgcctccctc  ctgcccctgc  tgcctctgat  cgtaggaatt  gaggagtgtc  ccgccttgtg
9721   gctgagaact  ggacagtggc  aggggctgga  gatgggtgtg  tgtgtgtgtg  tgtgtgtgtg
9781   tgtgtgcgcg  cgcgccagtg  caagaccgag  actgagggaa  agcatgtctg  ctggggtgtga
9841   ccatgtttcc  tctcaataaa  gttcccctgt  gacactcctc  ctgtctctct  tccagttctt
9901   ggcgatgggc  tgggagtggg  actgaatct   gacttagaga  ccctgacttt  ggacctctga
9961   gttagggccc  tgaactccct  aggtggctca  gtgccccgca  cgcaagactt  tgagtccagg
10021  tgaggccggg  gtcc
```

FIGURE 6F

H.sapiens Wilms tumor (WT1) gene promoter.   ACCESSION No. X74840   (SEQ ID NO:103)

```
   1 agcttgcagc cccagcccgg gccagccagg tacaggaggc cggactgcaa ccggttgctt
  61 ccctcccgtc gcgcctggcc gtcccacgct gcgccgtcgc tgctgcctcc tggcgcccct
 121 gggattttat acgcacctct gaaacacgct ccgctccggc cccggttct tctccttgcc
 181 taggggttgt ttcccaatag atactgactc ctttagaaga tccaaaaacc aaaccaaaaac
 241 accccctacc cgccccaaac acctgctctg gggcgcgggg gctgccaaac agagactaga
 301 cgaagggagt cagatttagc gaantcttcg agctcccaaa gattcgaaca ctaactcgcg
 361 cccgtggggcc gatggaggtt ctccctactc cactccttgg tcccttaac tggcttccgc
 421 ctcctggtca atcactgagc aaccagaatg gtatcctcga ccagggccac aggcagtgct
 481 cggcggagtg gctccaggag ttaccgctc ctgccgggct cgtatccaa accctcccct
 541 tcaccctcc tccccaaact gggcgccagg atgctccggc cggaatatac gcaggctttg
 601 ggcgtttgcc caagggtttt cttccctcct aaactagccg ctgttttccc ggcttaaccg
 661 tagaagaatt agatattcct cactggaaag ggaaactaag tgctgctgac tccaattta
 721 ggtaggcggc aaccgcttcc gcctggcgca aacctcacca agtaaacaac tactagccga
 781 tcgaaatacg cccggcttat aactggtgca actcccggcc accaactga gggacgttcg
 841 ctttcagtcc cgacctctgg aacccacaaa gggccacctc tttccccagt gacccccaaga
 901 tcatgccac tcccctaccc gacagttcta gaagcaagag ccagactcaa gggtgcaaag
 961 caagggtata cgcttctttg aagcttgact gagttctttc tgcgcttccc tgaagttccc
1021 gccctcttgg agcctacctg cccctcccctc caaaccactc ttttagatta acaaccccat
1081 ctctactccc accgcattcg accctgcccg gactcactgc ttacctgaac ggactctcca
1141 gtgagacgag gctcccacac tggcgaaggc caagaagggg aggtggggg agggttgtgc
1201 cacaccggcc agctgagagc gcgtgttggg gggtgtctcc caaggagca gcgcgcgctg
1261 ctccctcgga cccgccctca cccagctgc gagggcgccc ccaaggagca gcgcgcgctg
1321 cctggccggg cttgggctgc tgagtgaatg gagcggccga gcctcctggc tcctcctctt
1381 cccgcgcccg ccggcccctc ttatttgagc tttgggaagc tgagggcagc caggcagctg
```

FIGURE 7A

(SEQ ID NO: 103 (CON'T))

```
1441  gggtaaggag ttcaaggcag cgcccacacc cggggctct ccgcaaccc accgcctgtc
1501  cgctccccca cttcccgccc tccctcccac ctactcattc acccacccac ccacccagag
1561  ccgggacggc agcccaggcg cccggccccc gccgtctcct cgccgcgatc ctggacttcc
1621  tcttgctgca ggacccggct tccacgtgtg tcccggagcc ggcgtctcag cacacgctcc
1681  gctccgggcc tgggtgccta cagcagccag agcagcaggg agtccgggac ccgggcggca
1741  tctggccaa gttaggcgc gccgaggcca gcgctgaacg tctccagggc cggaggagcc
1801  gcggggcgtc cgggtctgag cctcagcaaa tgggctccga cgtgcgggac ctgaacgcgc
1861  tgctgcccgc cgtcccctcc ctgggtggcg gcggcggctg tgccctgcct gtgagcggcg
1921  cggcgcagtg ggcgccggtg ctggactttg cgcttcggct gccgcgccg tacgggtcgt
1981  tgggcggccc cgcgccgcca ccggctccgc ccgcacccc gccgcgccg cctcactcct
2041  tcatcaaaca ggagccgagc tggggcggcg cggagccgca cgaggaccag tgcctgagcg
2101  ccttcactgt ccacttttcc ggccagttca ctggcacagc cggagccgt cgctacggc
2161  ccttcggtcc tcctccgccc agccaggcgt catccggcca ggccaggatg tttcctaacg
2221  cgccctacct gcccagctgc ctcgagagcc agcccgctat tcgcaatcag ggtaagtagg
2281  ccggggagcg cccccta
```

FIGURE 7B

Estrogen Receptor (ER): Homo sapiens estrogen receptor beta gene, promoter region
and partial cds

Accession Number AF191544 (SEQ ID NO:16A)

```
   1 actataggc aCGCGtggtC GaCGgcccCGg gctggtattg atagatgcat tttcttcacc
  61 ctcacctatc tttttctgcc tgttggctta tggttgaaat tccttcatga CGgtttccat
 121 ttccagagat atcttgttaa caagtatata ccaccaaatg aagctgattt tttttttttt
 181 tttttttga gacagagtct CGctctgtCG cccaggctgg aatgcagtgg CGCGatcttg
 241 gctcactgca acctcCGcct cccatgttca agCGattctc ctgcctcagc ctcctgagta
 301 gctgggatta ctggcatgtg ccacCGCGtc cagccaattt ttgtattttt agtagagaCG
 361 aggtttcacc atgttggtca ggctggtctc aaactcctga cctCGtgatc cacctgcctc
 421 ggcctcccaa agtgctgaga ttataggtgt gagccaccat gcctggccat gaagctgatt
 481 tttttaaacc atcattaac atttctcca taaggtggca agacaggag gcatatgggg
 541 actgggtact ttgagagacc ccaggacagg agacaggag gctgagattg gcatgttgtc
 601 tgctgcagtt atttgccagC Gacacactct ttcCGtccaa actaacttct ctgcctcaag
 661 gacaggaga ctctgccttt caacctgaga gaaaccagga cacagctatt gttagctga taatgaaaat
 721 tggacttagg gtggggcagt ggagacttt cacagctatt gttagctga tgaagcagat
 781 gcttctccat ctttggagcc tgtcttcatt acctgtggac ctcatcttta tcaaccaga
 841 gcacacttgC Gtctctctat tttggctaaa caccaaacag ctgaggctgg tactgtaaaa
 901 ctttccctcc aaatgcccc cctCGtcttc ctctattaga gatctggatc acaaccctca
 961 aaaccatgt cccttatgcc acctgagtag atggtttgat gattaattag gcacagatgt
1021 gacactgggg gggtctcaca atggcctgtg ggtcacatgc tactttcctt ttcatttca
1081 tcagcaacag ctgccttaaa gccagttaag actgtggtcc tagtctCGca ccctgggct
1141 cctgctgggg tgggtgaggg gaacacccca ttaagctggg ggaactgggg ctgccaccag
1201 ggggCGCGag gggccttCGc cCGagaagag gggtgggcag gtgcctccag CGgagaaggg
1261 CGcCGtggcC Ggaggcacag gtctcccCGg tgccacttca agtgagttCG aggaagtacc
1321 tgggatcttt gatctaaCGC Gaaaggcctt cccagtgacc tcttgagggc tgagaaccca
1381 ctccctccac ctctagtcca CGgctttgcc actccaggg cCGaggttaC Gttttgctgct
1441 ggggatttga caaacccaaa gcctcctgg tttcaccact ggctcctta atcagacat
1501 ctgttctgaa tgacacttat gtgagtcagg ggctgaggaC GtgatcctCG aagtgtggtc
1561 cccagactgg ctgtatcagt gtCGgcatcc cccaggacct ggttgaaat gcatattctc
1621 aggccctact ccagacctct taaatctgag actgggctg catctgtgtCG
```

FIGURE 8A

```
1681  ccactatcct  tgtgggtgga  ccaggagtCG  gttCGagggt  gctcccactt  agaggtcaCG
1741  CGCGgcGtCG  ggCGttcctg  agacCGtCGg  gctccctggc  tCGgtcaCGt  gggctcaggc
1801  actactcccc  tctaccctcc  tctCGgtctt  taaaaggaag  aaggggctta  tCGTtaagtC
1861  Gcttgtgatc  ttttcagttt  ctccagctgc  tggctttttg  gacacccact  ccccCGccag
1921  gaggcagttg  caagCGCGga  ggctgCGaga  aataactgcc  tcttgaaact  tgcagggCGa
1981  ────────── tg  ggcCGgggag  ggaccaccG  agctgCGaCG  ggctctgggg
2041  ctgCGgggca  gggctggCGc  cCGgagcctg  agctgcagga  ggtgCGGctCG  cttccctcaa
2101  caggtggCGg  CGgggCGCGGC  GCGggagac  CGtgtgttt  atctgcaagc  ──────────
2161  atttttagag  aaggcaaggc  attataatga  cctttgtgcc  cattatactt  gcccaCGaat
2221  cttgagaac  attataatga  cctttgtgcc  tcttcttgca  agtgtttttc  tcagctgtta
2281  tctcaagac  ────────── gatataaa  aaactcacca  tctagcctta  attctcctc  ctcctacaac
2341  tgcagtcaat  ccatcttacc  cctggcacC  Ggctccatat  acataccttc  ctcctatgta
2401  gacagccacc  atgaatatcc  agcatgaca  ttctatagcc  ctgctgtgat  gaattacagc
2461  attcccagca  atgtcactaa  cttggaaggt  gggcc
```

FIGURE 8B

Unmethylated 288 BP

G ggTGtttttg agatTGtTGg   FUM 21 BP AT 60   (SEQ ID NO: 85)

TG agttgTGaTG ggttttgg   (SEQ ID NO: 86)

ccaaaacc CAtCAcaact CA RUM 20 BP AT 58   (SEQ ID NO: 87)

▇▇▇▇▇▇▇▇▇ FM 18 BP AT 60   (SEQ ID NO: 88)

▇▇▇▇▇▇▇▇▇   (SEQ ID NO: 89)

CGggaaaag taCGtgttCG t RM 20 BP AT 60   (SEQ ID NO: 90)

▇▇▇▇▇▇▇▇▇

FIGURE 8C